REMARKS

Status of Claims

Claims 48, 49, 55, 56 and 62-81 are pending in the application. Claims 48, 49, 55, 56 and 62-81 have been rejected. Claims 48, 55, 62-70, 72-76, and 78-81 have been amended. Claims 49-54, 56-61, 71, and 77 have been canceled without prejudice or disclaimer. In making this cancellation without prejudice, Applicants reserve all rights in these claims to file divisional and/or continuation patent applications.

CLAIM REJECTIONS

35 U.S.C. § 112 First Paragraph Rejections

In the Office Action, the Examiner rejected claims 48, 49, 55, 56 and 62-81 under 35 U.S.C. § 112, first paragraph. The Examiner alleged that the disclosure of the present invention does not reasonably provides enablement for a method of eliciting in a host an antibody as claimed in claims 48 and 62-65.

Applicants respectfully disagree. The subject specification as filed described a conserved epitope, defined by the presence of PEtN at the 3-position of Hep2 of a *Neisseria* inner core LPS, and described that vaccines containing the conserved epitope elicit antibodies that recognize NM immunotypes L1, L3, L7, L8, L9, L10, L11, and L12. "Recognize" and "bind" are recognized in the art to by synonyms in the context of raising antibody immune response and antibody recognition, and are utilized synonymously in the subject specification, as shown by the quotation below:

> "We have shown that MAb B5 can bind to the core LPS of wild-type encapsulated MC58 (B.15.P1.7,16 immunotype L3) organisms *in vitro* and *ex vivo*. An inner core structure recognized by MAb B5 is conserved and accessible in 26 of 34 (76%) of group B and 78 of 112 (70%) of groups A, C, W, X, Y, and *Z* strains" (page 21, first paragraph; emphasis added).

Further, the subject specification as filed described that MAb B5, an IgG_3 murine monoclonal antibody, was initially raised against *Neisseriastrain* H44/76 immunotype L3 (page 28, third paragraph). On page 31 (fourth paragraph) Applicants provided that MAb B5 reactivity was detected in 76% of group B *Neisseria meninigitidis* strains. Moreover, Applicants provided that MAb B5 possesses wide reactivity to serogroups A, B, C, W, X, Y, and Z (page 33, second paragraph). Table 2 on pages 41-42 demonstrates that MAb B5 is specifically reactive against L1, L3, L7, L8, L9, L10, L11, and L12. These results represent the most complete available collection of hyper-invasive lineages of *Neisseria meninigitidis* group B strains. Thus, Applicants demonstrated that use of an immunogenic segment of *Neisseria strain* H44/76 immunotype L3 which specifically elicits a host antibody response that is reactive against immunotypes L1, L3, L7, L8, L9, L10, L11, and L12 as claimed.

Further, the subject specification as filed described that the binding site of the elicited antibodies to the bacteria is inner core LPS:

> "The antibodies generated by the vaccine of this invention bind to inner core elements of the pathogenic target bacterium" (page 13, second full paragraph).

Accordingly, the subject specification described that the antibody binds to an inner core LPS of NM immunotypes L1, L3, L7, L8, L9, L10, L11, and L12.

In the Office Action, the Examiner rejected claims 76 and 78-81 under 35 U.S.C. § 112, first paragraph. The Examiner alleged that the disclosure of the present invention does not enable any person skilled in the art to which it pertains, to make and/or use the invention commensurate in scope with these claims.

Applicants respectfully disagree. As Applicants demonstrated MAb B5 is immuno-reactive against the majority of naturally occurring strains of *Neisseria meningitidis*. On page 31 (fourth paragraph) Applicants provided that MAb B5 reactivity was detected in 76% of group B *Neisseria meninigitidis* strains. Moreover, Applicants provided that MAb B5 possesses wide reactivity to serogroups A, B, C, W, X, Y, and Z (70%) (page 33, second paragraph). This disclosure provides conclusive data with respect to the efficacy of MAb B5 in possessing immuno-reactivity against the majority of naturally occurring strains of *Neisseria meningitidis*.

> "In summary, we report that a monoclonal antibody, designated B5, has identified a cross-reacting epitope on the LPS of the majority of naturally occurring, but genetically diverse strains of *Neisseria meningitidis*" (paragraph beginning on page 21; emphasis added).

Thus, the subject specification as filed described that the conserved epitope of the present invention is present on the majority of naturally occurring strains of NM, and is recognized by antibodies elicited by vaccines comprising the conserved epitope of the present invention.

The subject specification as filed described that immunogenic compositions of the present invention contain a conserved epitope useful in vaccination against *Neisseria*:

> "In a first aspect, the invention relates to a vaccine for the treatment of disease caused by *Neisseria* infection, the vaccine comprising an immunogenic component of *Neisseria* strains. The vaccine presents a conserved and accessible epitope that in turn promotes a functional and protective response" (page 5, fourth paragraph; emphasis added).

> "The epitope against which B5 reacts has been characterized and can be used to form the basis of a vaccine to prevent *Neisseria* infections" (page 6, third full paragraph).

Further, the subject specification clearly describes the conserved epitope as being characterized by the presence of PEtN at the 3-position of Hep2 of the inner core:

> "The immunogenic component of the present invention is typically only limited by the requirement for a PEtN moiety linked to the 3-position of HepII of the inner core" (page 9, fifth paragraph; emphasis added).

Further, the claims of the subject specification describe a vaccine comprising a conserved epitope, wherein the epitope is defined by the presence of PEtN at the 3-position of Hep2 of the inner core, and its use in immunization against *Neisseria* infection:

Thus, the subject specification clearly described and showed that antibodies elicited by the conserved epitope, or an immunogenic composition comprising same, recognize the NM immunotypes L1, L3, L7, L8, L9, L10, L11, and L12 and most of the NM strains. Accordingly, the subject specification described that vaccines comprising a conserved epitope, defined by the presence of PEtN at the 3-position of Hep2 of the inner core, are useful in immunization against NM immunotypes L1, L3, L7, L8, L9, L10, L11, and L12.

The subject specification as filed specifically enabled conserved epitopes of the present invention that are recognized in the presence of an outer core LPS:

> "The immunogenic component is suitably one which elicits an immune response in the presence and in the absence of outer core LPS" (paragraph beginning on page 7).

Accordingly, the subject specification as filed provides that the inner core LPS is accessible to the antibody in a presence of an outer core LPS thus enabling it.

Moreover, and contrary to the Examiner's assertion the subject specification as filed enabled accessibility of the antibody in a presence of a bacterial capsule. The disclosure provides that:

"We used a rabbit polyclonal antibody specific for Group B Neisseria meningitidis capsular polysaccharide obtained by immunising a rabbit six times sub-cutaneously with lysates of MC58 at 2-week intervals. The first and second immunisations contained Freund's complete adjuvant and Freund's incomplete adjuvant respectively. Serum was obtained from bleed. To increase specificity for the Group B capsular polysaccharide, rabbit polyclonal antibody (1 ml) was incubated overnight at 4°C with ethanol-fixed capsule-deficient MC58 (5x109 org./ml). This pre-adsorbed polyclonal antibody did not react with a capsule-deficient mutant of MC58 using immunofluorescence microscopy" (pages 25-26, emphasis added).

Accordingly, the subject specification as filed enabled that the inner core LPS is accessible to an antibody in a presence of a bacterial capsule.

Applicants assert that the subject specification as filed enabled immunogenic compositions comprising an inner core of a *Neisseria* LPS conjugated to a protein or peptide:

> "Vaccines of the present invention are preferably formulated vaccines in which any of the immunogenic components of the vaccine may be conjugated, and any suitable agent for conjugation may be used... Examples of agents for conjugation include proteins from homologous or heterologous species. In this way, the immunogenic component of the present invention forms a saccharide peptide conjugate" (paragraph beginning on page 13; emphasis added).

Accordingly, the subject specification as filed enabled an immunogenic composition comprising an inner core of a *Neisseria* LPS conjugated to a protein or peptide.

Applicants maintain that the subject specification as filed described and enabled immunogenic compositions comprising an inner core of a *Neisseria meningitidis* LPS:

> "Using a range of novel monoclonal antibodies, epitopes belonging to the inner core of *Neisseria meningitidis* have been identified which have been found to be accessible to the immune system, and which are capable of stimulating the production of function, protective antibodies" (page 5, last paragraph; emphasis added).

Accordingly, the subject specification as filed enabled the inner core of a *Neisseria* LPS.

In the Office Action the Examiner alleged that the only Neisseria LPS inner core species having a phsphoethanolamine moiety linked to position 3 of Hep II moiety of the inner core that has been used is the *galE* NM immunotype L3 LPS inner core lacking the outer core and that the specification is not enabling for methods of administration of an immunogenic composition comprising an outer core containing an inner core of a neisserial LPS.

Applicants respectfully disagree. On page 8 the specification provides that an immunogenic component of the invention elicits an immune response in the presence and in the absence of outer core LPS:

> "The immunogenic component is suitably one which elicits an immune response in the presence and in the absence of outer core LPS" (page 8).

On page 9, the specification provides detailed enabling disclosure concerning the sub-structural components of the outer core elements that may be present such as an outer core that comprises a galactose component- lacto-N-neotetraose.

> "There is no requirement for the immunogenic component to lack the outer core portion, or equivalent, of the LPS. The immunogenic component may comprise outer core elements having a galactose component, for example the terminal galactose residue of the lacto-N-neotetraose. In one suitably embodiment, the immunogenic component is derived from LPS and is free from other cellular material. Alternatively, cellular material may be present, and can take the form of live or killed bacteria" (page 9).

Applicants assert that the subject specification as filed enables one of skill in the art to utilize the methods of the invention comprising administering an immunogenic composition, comprising an outer core containing an inner core of a Neisserial LPS.

However, in order to expedite prosecution, Applicants amended claims 48, 55, 70, and 76 to include a composition which "is substantially free from outer core lipopolysaccharide".

In the Office Action the Examiner alleged that an animal model of passive protection that uses an avirulent *Neisseria meninigitidis* as the challenging or infecting strain is of little prophylactic significance.

Applicants respectfully disagree. Animal infection models are valuable for the development and preclinical assessment of meningococcal vaccines. It is only in animal models that interactions of the organism with the innate, humoral and cellular immune

systems can be assessed. Moreover, Applicants assert that infection of infant rats has been used to assess passive protection provided by sera raised against vaccine candidates or human vaccine sera. The specification of the present invention provide a valid recognized animal model that need not to contain an example in human subjects because the invention is disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation.

Moreover, Applicants assert that the art is such that the infant rat model is recognized as correlating to passive protection, moreover, the Examiner did not provide evidence that the model does not correlate.

In the Office Action the Examiner alleged that the Meningococcal conjugate vaccine of the invention is not enabled.

Applicants respectfully disagree. The disclosure in the present Application was followed by successful results in Meningococcal conjugate vaccines. Meningococcal conjugate vaccines are currently used to prevent infection caused by meningococcal bacteria. The vaccine contains four of the most common types of meningococcal bacteria.

The Food and Drug Administration approved the effective Quadrivalent Meningococcal Conjugate Vaccine (MCV4) (see http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5648a4.htm). Moreover, Applicants provided that a conjugate vaccine to meningococcal serogroup C is used for reducing the incidence of disease in young children in the United Kingdom. This data provides support for the efficacy of this technology (page 2, first paragraph).

As discussed hereinabove Applicants disagree with the Examiner's assertions, however, in order to expedite prosecution, Applicants amended claims 48, 55, 62-70, 72-76, and 78-81 and cancelled claims 49-54, 56-61, 71, and 77.

35 U.S.C. § 112 Second Paragraph Rejections

In the Office Action the Examiner rejected claims 48, 49, 55, 56, and 62-81 under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

First, the Examiner alleged that claims 48 and 55, as amended, and new claims 70 and 76, are vague, indefinite and confusing in the limitations: 'position 3 of a HepII moiety of said inner core' and 'an inner core LPS'.

Applicants respectfully disagree. However, in order to expedite prosecution, Applicants amended claims 48 and 55.

Second, the Examiner alleged that claims 48, 55, 70 and 76 are vague, indefinite, and inconsistent in the limitations: 'an inner core of a lipopolysaccharide' and 'an inner core LPS', because it is unclear how one differs from the other in terms of scope.

Applicants respectfully disagree. However, in order to expedite prosecution, Applicants amended claims 48, 55, and 70, and cancelled claim 76.

Third, the Examiner alleged that claim 48 is indefinite, confusing and inconsistent in scope in the limitations: 'an antibody ... recognizes *Neisseria meningitidis* immunotypes LI, L3, L7, L8, L9, L10, LI 1 and L12' (see lines 1-4) and 'said antibody binds to an inner core LPS of immunotypes LI, L3, L7, L8, L9, L10, LI 1 and L12'. While the latter phrase requires the antibody to bind to an inner core LPS of immunotypes LI, L3, L7, L8, L9, L10, LI 1 and L12, the former phrase is broader in scope which does not require the antibody to bind to an inner core LPS of immunotypes LI, L3, L7, L8, L9, L10, LI 1 and L12, but to recognize *Neisseria*

meningitidis immunotypes L1, L3, L7, L8, L9, L10, L11 and L1 2, which recognition can occur via binding to a non-inner core epitope within the LPS of said *Neisseria meningitidis* immunotypes.

Applicants respectfully disagree. However, in order to expedite prosecution, Applicants amended claim 48. Specifically, Applicants replaced the phrase 'an antibody ... recognizes *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L1 1 and L12,' in lines 1-4 of the claim with the phrase —"an antibody that specifically binds to inner core of lipopolysaccharide ...". Thus, the claim amendment reflects the Examiner's suggestion.

Fourth, the Examiner alleged that claims 62, 66, 71 and 78 are vague and indefinite in the limitation: "in a presence of an outer core LPS" because it is unclear what is encompassed in this limitation. Is this 'an outer core' of said Neisseria LPS, an outer core LPS of a meningococcus, an outer core LPS of a gonococcus, an outer core LPS of Shigella, or Francisella ?

Applicants respectfully disagree. However, in order to expedite prosecution, Applicants amended claim 62, 66, and 78, and cancelled claim 71.

Fifth, the Examiner alleged that claims 64, 67, 72 and 79 are vague and indefinite in the limitation: 'in a presence of a bacterial capsule', because it is unclear what is encompassed in this limitation.

Applicants respectfully disagree. However, in order to expedite prosecution, Applicants amended claims 64, 67, 72, and 79.

Sixth, the Examiner alleged that claims 64, 65, 68, 69, 74, 75, 80 and 81 are indefinite because these claims appear to lack proper antecedent basis in the limitation:

'said inner core *of & Neisseria* LPS'. These claims depend from claim 48, 55, 70, or 76, which already recites "a *Neisseria* lipopolysaccharide (LPS)".

Applicants respectfully disagree. However, in order to expedite prosecution, Applicants amended claims 64, 65, 68, 69, 74, 75, 80 and 81.

Seventh, the Examiner alleged that claims 48, 55, 70 and 76 are indefinite in the limitation: 'capable of conferring passive protection against a galE mutant of an L3 immuntype *Neisseria meningitidis* strain' because it is unclear in whom the recited antibody is capable of conferring passive protection against a *galE* mutant of an L3 immunotype *Neisseria meningitidis* strain.

Applicants, respectfully disagree. Applicants provided an infant rat model, considered by those skilled in the art, valuable for the development and preclinical assessment of meningococcal vaccines. Applicants maintain that the infant rat model provides valuable, clear, *in-vivo* information concerning the interactions of the vaccine with the innate, humoral and cellular immune systems. Specifically, Applicants assert that infection of infant rats for assessing passive protection has been described in such detail that the claim limitation of claims 48, 55, 70, and 76 is definite.

Eighth, the Examiner alleged that claims 49 and 62-65, which depends from claim 48; claims 56 and 66-69, which depend from claim 55; claims 71-75, which depend from claim 70; and claims 77-81, which depend from claim 76, are indefinite because of the indefiniteness identified in the base claims.

Applicants respectfully disagree. However, in order to expedite prosecution, Applicants amended claims 62-65 and cancelled claim 49.

Thus, the pending claims do not contain new matter over the subject specification as filed, and therefore are in compliance with the requirements of 35 U.S.C. § 112. Applicants therefore respectfully request that the rejection be withdrawn.

35 U.S.C. § 102 Rejections

Further, the Examiner rejected claims 48, 49, 55, 56, and 62-81 under 35 U.S.C. § 102(b) in view of van der Ley et al. as evidenced by Poolman JT. and Vogel et al. or van der Ley et al.

In the Office Action, the Examiner alleged that van der Ley et al. taught a method of immunizing experimental animals by administering immunogenic meningococcal *galE* mutant LPS that elicited antibodies recognizing novel epitopes in the inner-core region. One of the antibodies thus elicited binds to the *galE* mutant and wild-type strains.

Applicants respectfully disagree. Applicants assert that the system described by van der Ley et al. is materially different from the claims of the subject Application. Thus, van der Ley et al. does not qualify as a 102 reference.

Specifically, the experiments performed by van der Ley et al. do not include elicitation of antibodies. The experiments described are limited to the basic ability of certain monoclonal antibodies to screen for engineered strains of *Neisseria meningitidis* that are defective in LPS biosynthesis (see page 1118 in van der Ley et al.). Moreover, the monoclonal antibodies used by van der Ley et al. were initially raised after immunization with outer membrane complexes (OMCs) wherein the claims of the present Application are directed at eliciting in a host an antibody that specifically binds **to an inner core** of lipopolysaccharide by administering to a host an immunogenic composition comprising an inner core of a Neisseria lipopolysaccharide (LPS) **substantially free from outer core lipopolysaccharide**. Thus, the Examiner erred in his assertion that the methods disclosed by van der Ley et al. include immunizing experimental animals by administering immunogenic meningococcal *galE* mutant LPS that elicited antibodies recognizing novel epitopes in the inner-core region. One of the antibodies thus elicited binds to the *galE* mutant and wild-type strains.

Moreover, the present Application provides that "designated MAb B5, was obtained by immunizing mice with a *galE* mutant of Neisseria meningitides H44/76 (B.15.P. 1.7.16 **immunotype L3**) (see page 21). The HC-L3 and ES-L3 strains of van der Ley et al. are stable L3 **negative** mutants containing an erythromycin resistance marker. These strains are different from the strains described in the present Application which are not erythromycin resistant strains and/or **stable L3 negative mutants**. Testing of MAbs of the present Application was carried out by screening against purified LPS from ***Neisseria meningitidis* L3** (see Figure 1), and Salmonella typhimurium Ra and Rc mutants. Thus, the Examiner erred in his determination with regard to the equivalency of the bacterial strains used by van der Ley et al. and the bacterial strains used in the present Application.

The Examiner further alleged that van der Ley et al. disclosed a method of immunizing experimental host animals with an outer membrane complex preparation from a *galE* mutant of strain H44/76 (L3 immunotype) of *Neisseria meningitidis* mixed in an adjuvant, and the selection of positive hybridomas using galE LPS as the coating antigen in ELISA.

Applicants assert that amended claims 48, 55, 70, and 76 include administering to a host an immunogenic composition comprising an "inner core of a Neisseria lipopolysaccharide (LPS)" **"substantially free from outer core lipopolysaccharide"**. Thus, van der Ley et al. LPS-containing immunogen administered to experimental animals is entirely different from the *Neisseria meningitidis* strain of the present invention derived from the *galE* mutant of the H44/76 strain

In the Office Action the Examiner further alleged that the prior art LPS-containing immunogen derived from the *galE* mutant is identical H44/76 strain of *Neisseria meningitidis* as that used by Applicants.

Applicants respectfully disagree. In relying upon the theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the disclosure of the applied prior art. The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that

result or characteristic (MPEP Section 2112). Applicants provide that inherency may not be established by probabilities or possibilities. Applicants assert that the Examiner failed to meet its burden of proving inherent anticipation of van der Ley et al. with respect to a phosphoethanolamine moiety linked to position 3 of HepII moiety.

Applicants assert that Vogel et al., Poolman JT., van der Ley et al. 1995, and van der Ley et al. 1996 provide no data disclosing or suggesting elicitation of antibodies against a *galE* mutant of an **L3 immunotype** *Neisseria meningitidis* strain, as recited in the amended claims. Thus, van der Ley et al. 1996 neither discloses nor suggests the subject matter of the subject claims.

In view of the foregoing amendments and remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 50-3355.

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Dated: January 14, 2008

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